Is language impairment more common than executive dysfunction in amyotrophic lateral sclerosis?

Lorna J Taylor,1,2 Richard G Brown,1,2 Stella Tsermentseli,1,3 Ammar Al-Chalabi,2,4 Christopher E Shaw,2,4 Catherine M Ellis,5 P Nigel Leigh,6 Laura H Goldstein1,2

ABSTRACT

Background Systematic explorations of language abilities in patients with amyotrophic lateral sclerosis (ALS) are lacking in the context of wider cognitive change.

Methodology Neuropsychological assessment data were obtained from 51 patients with ALS and 35 healthy controls matched for age, gender and IQ. Composite scores were derived for the domains of language and executive functioning. Domain impairment was defined as a composite score ≤5th centile relative to the control mean. Cognitive impairment was also classified using recently published consensus criteria.

Results The patients with ALS were impaired on language and executive composite scores. Language domain impairment was found in 43% of patients with ALS, and executive domain impairment in 31%. Standardised language and executive composite scores correlated in the ALS group (r=0.68, p<0.001). Multiple regression analyses indicated that scores on the executive composite accounted for 44% of the variance in language composite scores.

Conclusions Language impairments are at least as prevalent as executive dysfunction in ALS. While the two domains are strongly associated, executive dysfunction does not fully account for the profile of language impairments observed, further highlighting the heterogeneity of cognitive impairment in non-demented patients with ALS.

INTRODUCTION

The clinical presentation of amyotrophic lateral sclerosis (ALS) extends beyond the motor system, and studies have reported cognitive impairments of varying severity. While a minority of patients meet criteria for the frontotemporal dementia (FTD) and/or primary progressive aphasia (PPA) subtypes of frontotemporal lobar degeneration (FTLD), approximately one-third show cognitive impairments of a milder nature.2–4 Executive dysfunction, a negative prognostic indicator of survival in ALS,5 has been the most commonly investigated cognitive domain in non-demented patients with ALS. Studies have often reported impairments in fluency, set-shifting, attention and inhibition.6–8 Recent consensus criteria have defined cognitive impairment in ALS on the basis of impaired scores (≤5th centile of age- and education-matched controls) on at least two measures of executive functioning.3 Cognitive impairments in ALS are not, however, restricted to the executive domain.4 A number of studies have reported impairments on tasks of language function including confrontation naming, single word and syntactic comprehension, and verb processing.4,9,10 It remains unclear whether this reflects an aphasia-like impairment11 or is secondary to executive dysfunction.12 There have been comparatively few investigations of language in non-demented patients with ALS and consequently the nature and frequency of language impairment occurrence has not been fully characterised. This study aimed to investigate the prevalence and profile of language change in ALS and the relationship with executive function.

MATERIALS AND METHODS

Participants Patients were recruited primarily from The King’s Motor Neurone Disease (MND) Care and Research Centre, London, UK. Additional patients were recruited from MND Care and Research Centres in Cambridge, Newcastle and Manchester, UK. Healthy control participants were recruited through a volunteer database (http://mindsearch.iop.kcl.ac.uk/). Ethics approval was obtained from King’s College Hospital Research Ethics Committee (07/H0808/156). Appropriate institutional approvals were obtained to permit recruitment from additional centres. Informed written consent was obtained from all participants, consistent with the Declaration of Helsinki.

Exclusion criteria for all participants were not having English as a first language, cerebrovascular disease, hypertension, diabetes, history of head injury and current prescription of psychoactive medication. We included right-handed patients, aged <75 years with evidence of probable or definite ALS.13 Additional patient exclusion criteria included respiratory weakness (forced vital capacity < 70%), familial history of ALS, and a clinical diagnosis of comorbid dementia. Where recruited patients showed clinically evident behavioural and/or cognitive impairment at the initial interview, FTLD diagnostic criteria14 were applied to identify patients with FTD, PPA (either progressive non-fluent aphasia or semantic dementia). Patients meeting criteria were excluded.

Domains of language and executive functioning were assessed (table 1) as part of a broader battery of tests including memory function (see online supplementary material). Current and premorbid IQ were assessed using the Wechsler Abbreviated Scale
of Intelligence\(^{15}\) and Wechsler Test of Adult Reading (WTAR),\(^{16}\) respectively. The Hospital Anxiety and Depression Scale (HADS)\(^{17}\) measured symptoms of anxiety and depression. In the patients, functional abilities were assessed using the Amyotrophic Sclerosis Functional Rating Scale Revised (ALSFRS-R).\(^{18}\) Patients were assessed in their homes, and control participants at the Institute of Psychiatry. Assessments were conducted over two sessions, approximately 1 week apart. A fixed test order was used to attempt to control for effects of fatigue and between-test interference across the two groups.

To avoid undertaking multiple between-group comparisons using individual tests, composite scores were calculated from selected indices for the language and executive domains (table 1). As successful completion of the assessment measures may depend on a combination of executive and linguistic abilities (eg, Hayling Sentence Completion Test, phonemic and semantic verbal fluency), total domain score–individual test score correlations were examined to determine the allocation of measures to cognitive composite scores. Standardised z scores for each test were calculated by subtracting the mean score of controls from the participant’s score and then dividing the difference by the control group SD. All measures were adjusted such that a negative score indicated worse performance. z Scores in each domain were summed, and divided by the number of tests completed to give the composite score. Impairment was defined as a composite score ≤5th centile (~1.64 SDs) below the control mean. Raw scores were used for secondary analyses to consider the variation in impairment across individual measures. As an alternative indicator of overall impairment, the consensus criteria requiring impairment on two or more tests of executive function were also applied, and extended to include classification of language impairment following impairment evident on two or more tests of language functioning.

### Statistical analysis

The data were analysed using SPSS V.17. Demographic, clinical and cognitive characteristics were reported as percentages for categorical data and means for continuous variables. Between-group comparisons were undertaken using t tests or multivariate analysis of covariance. Categorical data were analysed using \(\chi^2\) tests. Pearson’s correlations and multiple regression analyses were used to examine the relationships between executive and language composite scores. Any outliers were identified and transformed to reduce their impact on the analysis. All tests were two-tailed, and statistical significance was set at \(p<0.05\).

## RESULTS

### Demographic and clinical characteristics

Fifty-one patients with ALS and 35 healthy controls participated in the study. There were no significant differences between the groups with respect to gender distribution, age and years of education, current IQ or estimated premorbid IQ (table 2). Six patients with ALS were unable to complete the WTAR because of dysarthria, so premorbid IQ estimates were obtained for 45 patients with ALS. Patients had higher mean anxiety, depression and total HADS scores than controls, and the HADS total score was used as a covariate for subsequent between-group analyses. However, although participants’ HADS scores were not

### Table 1 Test indices included in cognitive composites

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measures contributing to the composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive functioning</td>
<td>Phonemic Verbal Fluency Index (VFI)(^1): words beginning with ‘S’ and 4-letter words beginning with ‘C’, adjusted for motor disability</td>
</tr>
<tr>
<td></td>
<td>Semantic VFI(^2): ‘animal’ and ‘food’ words adjusted for motor disability</td>
</tr>
<tr>
<td></td>
<td>Hayling Sentence Completion Test(^3): latency score (time difference between completion of unconnected and connected sentences)</td>
</tr>
<tr>
<td></td>
<td>Brixton Spatial Anticipation Test(^4): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Card Sorting test from Delis–Kaplan Executive Function System(^5): sorting score (maximum—score) and description score (maximum—score)</td>
</tr>
<tr>
<td>Language</td>
<td>Cookie Theft Picture (from the Boston Diagnostic Aphasia Examination)(^6): Complexity Index</td>
</tr>
<tr>
<td></td>
<td>British Picture Vocabulary Scale-II(^7): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Test of Reception of Grammar-second edition(^8): number of blocks failed</td>
</tr>
<tr>
<td></td>
<td>Boston Naming Test(^9): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Category Specific Names Test(^10): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Oral and Written Naming of Nouns and Verbs(^11): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Judgement of Synonyms Subtest from Psycholinguistic Assessment of Language Processing in Aphasia(^12): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Graded Difficulty Spelling Test(^13): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Pyramids and Palm Trees(^14): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Kissing and Dancing Test(^15): total number of errors</td>
</tr>
<tr>
<td></td>
<td>Spot the Word Test(^16): total number of errors</td>
</tr>
</tbody>
</table>

### Table 2 Demographic characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Controls (n=35)</th>
<th>t (df)/(\chi^2) (df)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.84 (9.06)</td>
<td>59.31 (7.57)</td>
<td>0.28 (84)</td>
<td>0.777</td>
</tr>
<tr>
<td>Education (years)</td>
<td>13.75 (3.25)</td>
<td>14.71 (2.85)</td>
<td>−1.42 (86)</td>
<td>0.157</td>
</tr>
<tr>
<td>HADS Depression</td>
<td>4.63 (3.36)</td>
<td>1.80 (2.05)</td>
<td>4.50 (84.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS Anxiety</td>
<td>3.67 (2.63)</td>
<td>1.69 (1.51)</td>
<td>4.02 (84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HADS Total</td>
<td>8.33 (5.80)</td>
<td>3.49 (3.30)</td>
<td>4.46 (84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current IQ (WASI)</td>
<td>119.21(10.58)</td>
<td>121.06 (5.46)</td>
<td>−0.97 (62.29)</td>
<td>0.334</td>
</tr>
<tr>
<td>Premorbid IQ (WTAR)</td>
<td>110.33 (6.49)</td>
<td>111.22 (4.08)</td>
<td>−1.94 (75.03)</td>
<td>0.266</td>
</tr>
<tr>
<td>Gender, N (%) male</td>
<td>29 (57%)</td>
<td>20 (57%)</td>
<td>0.00 (1)</td>
<td>0.979</td>
</tr>
</tbody>
</table>

ALS, amyotrophic lateral sclerosis; HADS, Hospital Anxiety and Depression Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WTAR, Wechsler Test of Adult Reading.
modified to account for physical impairment, the scores did not indicate clinically relevant levels of depression or anxiety. The mean ALSFRS-R score at the time of neuropsychological assessment was 33.15 (SD 9.07). Seventy-five per cent of patients had limb-onset and 25% bulbar-onset disease, consistent with typical phenotype frequencies. The average time since onset of symptoms was less than 3 years, with an average delay from symptom onset to diagnosis of ~12 months. Seventy per cent of patients with ALS were taking riluzole at the time of assessment.

Profile and prevalence of executive and language impairment
Multivariate analysis of covariance, with HADS total score entered as a covariate, revealed that the patient mean scores were significantly lower overall (more impaired) \((F(4,79)=4.47, p<0.05)\). Univariate contrasts revealed that the mean patient scores were significantly lower for the executive domain \((-0.42, SD=0.70\) compared with \(0.0, SD=0.37\) for controls; \(F(1,83)=5.67, p=0.02,\) partial \(\eta^2=0.064\)) and for the language domain \((-0.98, SD=1.31\) compared with \(0.0, SD=0.53\) for controls; \(F(1,83)=8.42, p=0.005,\) partial \(\eta^2=0.092\)).

Based on the 5% cut-off derived from the control sample, 31% of the patients with ALS were classified as impaired on the executive composite and 43% on the language composite. Of the 23 patients with impairment on the language composite, 13 (55.6%) had executive composite scores within the normal range. Pearson’s \(\chi^2\) analysis revealed no relationship between bulbar-onset disease and impairment in the language \((\chi^2(1)=0.81, p=0.37\) and executive domains \((\chi^2(1)=0.003, p=0.96\).

Analysis of variance revealed no significant differences in age \((F(3,51)=0.462, p=0.710,\) partial \(\eta^2=0.029)\), HADS scores \((F(3,51)=1.223, p=0.312,\) partial \(\eta^2=0.072)\), years of education \((F(3,51)=5.67, p=0.080,\) partial \(\eta^2=0.082)\), months since onset of illness \((F(3,51)=0.930, p=0.434,\) partial \(\eta^2=0.056)\) and ALSFRS-R scores \((F(3,51)=1.70, p=0.180,\) partial \(\eta^2=0.098)\) between the different cognitive profile groups (no impairment on executive or language composites, impairments on executive and language composites, impairments on the executive composite only, impairment on the language composite only).

Applying the consensus criteria of impairment on two or more tests of executive function, 13 (25%) patients were classified as cognitively impaired. Applying and extending the criteria to the language tests, 20 (39%) were impaired. Of these, seven (35%) performed within the normal range on all measures of executive functioning. Table 3 shows the raw scores on individual language and executive function tests and the proportion of patients meeting criteria for impairment (NB higher scores indicating worse performance). Executive function testing were differentially sensitive to impairment (6–26.5% of the patients were found to be impaired on individual measures) as were the language tests, with impairment noted in 4–49%, depending on the measure.

Relationship between executive and language domains within the ALS group
To normalise the distributions and equalise variance for within-group analysis, composite scores were restandardised for the ALS participants using the group means and SDs. Pearson’s correlations examining associations between composite scores in the ALS group revealed a relationship between the severity of impairment measured by the executive and language \((r=0.68, p<0.001)\) composites. A linear regression analysis indicated that the executive composite scores accounted for 44% of the variance in the language composite scores (standardised \(\beta=0.63, 95\% CI 0.46 to 0.96, t(51)=5.80, p<0.001)\).

DISCUSSION
The findings of this study are broadly consistent with the extensive literature indicating executive dysfunction in approximately

---

**Table 3** Measures of executive and language functioning: raw scores, SDs and number (and percentage) of patients with ALS impaired on each test

<table>
<thead>
<tr>
<th>Test</th>
<th>Raw score mean (SD)*</th>
<th>ALS</th>
<th>Controls</th>
<th>(F (df))</th>
<th>(p) Value</th>
<th>No of ALS patients impaired (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D-KEFS (sorting score)</td>
<td>1.39 (1.46)</td>
<td>0.60 (1.03)</td>
<td>5.47 (1.82)</td>
<td>0.028</td>
<td>13/49 (26.5)</td>
<td></td>
</tr>
<tr>
<td>D-KEFS (description score)</td>
<td>39.91 (22.25)</td>
<td>36.03 (15.05)</td>
<td>0.60 (1.82)</td>
<td>0.441</td>
<td>3/49 (6)</td>
<td></td>
</tr>
<tr>
<td>Hayling (latency)</td>
<td>24.98 (22.43)</td>
<td>22.97 (21.15)</td>
<td>0.24 (1.84)</td>
<td>0.878</td>
<td>6 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Brixton (errors)</td>
<td>15.67 (4.67)</td>
<td>13.89 (3.36)</td>
<td>3.74 (1.84)</td>
<td>0.042</td>
<td>13 (25)</td>
<td></td>
</tr>
<tr>
<td>Phonemic VFI</td>
<td>8.99 (9.92)</td>
<td>7.24 (7.03)</td>
<td>3.54 (1.84)</td>
<td>0.043</td>
<td>13 (25)</td>
<td></td>
</tr>
<tr>
<td>Semantic VFI</td>
<td>2.11 (0.99)</td>
<td>1.71 (0.95)</td>
<td>1.47 (1.84)</td>
<td>0.228</td>
<td>9 (18)</td>
<td></td>
</tr>
<tr>
<td>BNT (errors)</td>
<td>4.05 (4.01)</td>
<td>2.37 (1.93)</td>
<td>1.37 (1.84)</td>
<td>0.224</td>
<td>13 (25)</td>
<td></td>
</tr>
<tr>
<td>TROG (blocks failed)</td>
<td>1.98 (1.64)</td>
<td>0.91 (0.81)</td>
<td>5.79 (1.84)</td>
<td>0.018</td>
<td>18 (35)</td>
<td></td>
</tr>
<tr>
<td>PPT (errors)</td>
<td>1.45 (1.61)</td>
<td>0.74 (1.22)</td>
<td>1.98 (1.84)</td>
<td>0.162</td>
<td>7 (13.5)</td>
<td></td>
</tr>
<tr>
<td>KDT (errors)</td>
<td>2.66 (2.27)</td>
<td>0.74 (1.38)</td>
<td>13.45 (1.84)</td>
<td>&lt;0.001</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Synonym Judgement (errors)</td>
<td>3.78 (4.32)</td>
<td>2.00 (2.07)</td>
<td>5.53 (1.84)</td>
<td>0.021</td>
<td>10 (19)</td>
<td></td>
</tr>
<tr>
<td>Verb–Noun (errors)</td>
<td>1.06 (1.70)</td>
<td>0.72 (1.14)</td>
<td>1.18 (1.62)</td>
<td>0.295</td>
<td>5/44 (11.5)</td>
<td></td>
</tr>
<tr>
<td>BPVS (errors)</td>
<td>11.50 (7.24)</td>
<td>5.77 (2.79)</td>
<td>12.09 (1.82)</td>
<td>&lt;0.001</td>
<td>25 (49)</td>
<td></td>
</tr>
<tr>
<td>CSNT (errors)</td>
<td>21.80 (14.73)</td>
<td>16.60 (7.10)</td>
<td>11.3 (1.84)</td>
<td>0.029</td>
<td>12 (23)</td>
<td></td>
</tr>
<tr>
<td>Cookie Theft Picture (Complexity Index)</td>
<td>1.88 (0.31)</td>
<td>1.79 (0.37)</td>
<td>0.94 (1.78)</td>
<td>0.759</td>
<td>2/46 (4)</td>
<td></td>
</tr>
<tr>
<td>STW (errors)</td>
<td>7.70 (4.50)</td>
<td>5.06 (3.16)</td>
<td>4.74 (1.84)</td>
<td>0.032</td>
<td>12 (23)</td>
<td></td>
</tr>
<tr>
<td>GDST (errors)</td>
<td>5.58 (2.29)</td>
<td>3.57 (2.72)</td>
<td>6.32 (1.84)</td>
<td>0.014</td>
<td>8 (15.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- ALS, amyotrophic lateral sclerosis; BNT, Boston Naming Test; BPVS, British Picture Vocabulary Scale; CSNT, Category-Specific Names Test; D-KEFS, Delis–Kaplan Executive Function System; GDST, Graded Difficulty Spelling Test; KDT, Kissing and Dancing Test; PPT, Pyramids and Palm Trees Test; VFI, Verbal Fluency Index; TROG, Test for the Reception of Grammar; STW, Spot the Word Test.
- *Higher scores reflect greater impairment. In instances where not all participants were able to complete the measure, the number completing the test is reported.*
The presence of notable cognitive de-
impairment. Failure to include language
impairment, either combined with executive impairment
or in isolation, suggests that published screening tools and con-
glomerate criteria for diagnosing mild cognitive impairment may
be at least as common as executive dysfunction, with 43% of
patients showing impairment on the composite measure. A
similar pattern was observed when extended consensus criteria
were used, with impairment of 25% and 39% in executive and
language domains, respectively.

The significant association between the severity of language
and executive dysfunction and the common co-occurrence of
impairment in the two domains is consistent with previous
research that has interpreted impaired language abilities in non-
demented patients with ALS as being a consequence of execu-
tive dysfunction rather than of a primary linguistic disorder.2 12
Although the precise mechanism by which executive dysfunction
affected language is unclear, aspects of linguistic processing have
been related to frontal pathology in ALS.33 Conversely, impair-
ments in the executive domain noted may partly reflect language
dysfunction and be interpreted as a consequence of impaired
linguistic functions. While recognising the co-occurrence and
association between impairment in the two cognitive domains,
the results of this study suggest that the two deficits are, in part,
dissociable. The two domains shared only 44% of variance in
terms of performance, and over 40% of patients impaired on the
language composite performed with the normal range on the
executive composite, with a similar figure (35%) when impairment was based on the consensus criteria.

The present findings suggest that cognitive impairment in
ALS is heterogeneous, with some patients showing a predomin-
antly dysexecutive profile, others showing a predominantly lin-
guistic profile, and some a mixed pattern. This is similar to the
case of single-domain and multiple-domain mild cognitive
impairment seen in the prodromal stages of Alzheimer’s disease
and other dementias.34 It is also consistent with investigations
of FTLD in patients with ALS that have highlighted both overlap
and independence of FTD and PPA subtypes.35

The increasing awareness of mild cognitive change in non-
demented patients with ALS has led to the development of brief
screening tools36–38 and the publication of consensus criteria for
optimal assessment of cognitive change.3 These criteria recom-
end that non-demented patients with ALS be considered as
cognitively impaired following performance on standard neuro-
psychological testing ≤5th centile, compared with age-
and education-matched norms, on two or more distinct cognitive
tests sensitive to executive functioning. The significance of lan-
guage impairment, either combined with executive impairment
or in isolation, suggests that published screening tools and con-
sensus criteria for diagnosing mild cognitive impairment may
insufficiently address the heterogeneity of cognitive change in
non-demented patients with ALS. Failure to include language
dysfunction in the definition of cognitive change may therefore
lead to underestimations of the prevalence rates of cognitive
impairment.

In addition to implications for the formal assessment of cog-
nitive change in ALS clinics, the findings are important when the
more general awareness and understanding of cognition in
ALS are considered. Increasing awareness of cognitive change is
of importance to people with ALS and in the care of individuals
with ALS, potentially reducing carer and patient anxiety about
the presence of notable cognitive deficits. This study suggests
that the observed heterogeneity in cognitive change seen in ALS
needs to be further accepted in clinical practice to facilitate a
model of effective management of patients with ALS that
includes consideration of language impairments as well as executive dysfunction.

The findings of this study may inform future neuroimaging
and pathological investigations. The observed heterogeneity of
cognitive presentation may reflect variable involvement of
frontal and temporal structures subserving executive and lan-
guage functioning. Furthermore, and in consideration of neuroi-
maging investigations that have noted white matter tract
abnormalities in frontotemporal white matter association
tracts,33 it is also feasible that the cognitive presentation in ALS
may be determined by differential degeneration of white matter.
Future research combining in vivo neuropsychological assess-
ment, neuroimaging and postmortem pathological investigation
is required to determine the pathological processes and neuro-
anatomical changes in non-demented patients with ALS with
varying cognitive presentations. Previous research has high-
lighted the role of genetic factors in determining the cognitive
profile of patients with ALS with mild cognitive change.8 Given
the present study’s identification of differing presentations of
cognitive change, future research could investigate the role of
genetic risk factors, as has been undertaken in studies of FTLD.

This study has several limitations that may affect the interpret-
atation of the results and generalisations to the wider ALS popu-
lation, including use of prevalence rather than incidence
sampling, and recruiting from specialist centres rather than
community settings. This is a limitation of the majority of
neuropsychological investigations of ALS, although some
population-based studies have also confirmed the heterogeneity
of cognitive impairment in ALS.4 While our exclusion criteria
were important in ensuring that cognitive impairment could not
be better explained by comorbid conditions and disease-related
factors, the application of such criteria may render the present
sample less representative of the ALS population as a whole, but
more informative with respect to the effects of ALS on cogni-
tion. Owing to the exclusion of participants with a diagnosis of
FTLD, the prevalence of language and executive impairment
reported in this study relates only to mild impairments in non-
demented patients with ALS, and the study is unable to
comment on the incidence rates or nature of executive and lan-
guage impairment of increasing degrees of severity in the wider
ALS population.

Interpretations drawn from this study may be limited by the
use of cognitive composite scores calculated from several hetero-
geneous assessment measures. While this avoids type I errors
associated with multiple between-group comparisons and allows
a focus on overall rates of impairment in executive and language
domains, inspection of patient performance on individual mea-
sures (presented for the interested reader in table 3) would
provide additional insights into the profiles of cognitive impair-
ment seen in non-demented patients with ALS. In addition, the
attempt to assess several areas of language functioning means
that the language composite score included a greater number of
language tests (relative to executive tests included in the execu-
tive composite), potentially rendering the study more sensitive
to language than executive impairments.

In addition to the language and executive tests, a number of
other tests were conducted as part of a comprehensive neuro-
psychological examination. A comparable memory domain
score did not differentiate the ALS and healthy control groups,
and the proportion of ALS and healthy control participants who
showed impaired performance on the memory composite score
did not significantly differ (see online supplementary material).
Data were not considered further. The memory composite score
included indices from a small number of memory assessments (relative to the language and executive composites), and a greater number of memory tests may have increased the study’s sensitivity to detect memory impairments.

These limitations notwithstanding, our identification of language impairment that cannot be explained by executive dysfunction in a proportion of patients with ALS raises questions about the future assessment and ascertainment of mild cognitive change in ALS. Our findings also highlight the need to consider revising the current consensus criteria for the identification of cognitive impairment in ALS.

Acknowledgements The study was supported by the Medical Research Council, the Motor Neurone Disease Association, UK and the Institute of Social Psychiatry. This work was also supported by the European Community’s Health Seventh Framework Programme (FP7/2007–2013) (259867 to AA-C and CES). We would also like to acknowledge Dr J Ealing, Dr C Allen and Dr T Williams and the Dementias & Neurodegenerative Diseases Research Network (DeNDRoN) for facilitating recruitment at each centre. RGB, AA-C, CES and LHG receive salary support from the National Institute for Health Research (NIHR) Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust and King’s College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Contributors LJT contributed to the design of the study, the collection of data, analysed the data, and wrote the manuscript. RGB supervised the study and revised the manuscript. MT contributed to the process of recruitment and data collection. AA-C, CES, PNL and CME revised the manuscript from a clinical perspective. LHG supervised the study, was responsible for the conception of the project, and revised the manuscript.

Funding The study was supported by the Medical Research Council, the Motor Neurone Disease Association, UK and the Institute of Social Psychiatry. This work was also supported by the European Community’s Health Seventh Framework Programme (FP7/2007–2013) (259867 to AA-C and CES). RGB receives research support from Parkinson’s UK via the National Institute for Health Research (UK), Medical Research Council (UK), Alzheimer Society (UK), Alzheimer Research Trust (UK), and the Edmund J Safra Foundation (Switzerland). AA-C receives research support from the Motor Neurone Disease Association UK, the ALS Association and the ALS Therapy Alliance. CES receives research support from the Motor Neurone Disease Association UK, the Medical Research Council, the Wellcome Trust and Psychiatry Research Trust. PNL has received research support from the Motor Neurone Disease Association and the Wellcome Trust UK. LHG receives research support from Department of Health/National Institute for Health Research (NIHR) UK and the Motor Neurone Disease Association UK. She has also received support from Epilepsy Research UK, the Institute of Social Psychiatry and the Wellcome Trust UK.

Competing interests AA-C receives royalties from the publication of The Brain (Oneworld Publications) and The Genetics of Complex Human Diseases (Cold Spring Harbor Laboratory Press for a book). RGB has received travel expenses and honoraria for speaking and educational activities not funded by industry, and for activities funded by the following companies: UCB Pharma, GSK, Abbott Healthcare Products. CES has received travel expenses and honoraria acting as a consultant to GlaxoSmithKline. PNL has received honoraria or consultancy fees and travel expenses from Sanofi Aventis, GlaxoSmithKline (GSK), Acceleron, Cytokinetics, Neurona, and is or has been a member of advisory boards for GSK, Acceleron, Cytokinetics, Neurona. LHG serves on the Scientific Awards Panel for Epilepsy Action (UK), has received travel expenses and honoraria for speaking and educational activities not funded by industry, receives royalties from the publication of Clinical Neuropsychology (Wiley, 2004, 2012) and The Clinical Psychologist’s Handbook of Epilepsy ( Routledge, 1997). Ethics approval King’s College Hospital Research Ethics Committee. Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Supplementary Material:

Table 1: Test indices included in the Memory composite

<table>
<thead>
<tr>
<th>Measures contributing to the Memory Composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendrick Object Learning Test (KOLT)¹: Total number of errors</td>
</tr>
<tr>
<td>Words subtest of Recognition Memory Test (RMT)²: Maximum score – total number of stimuli recalled</td>
</tr>
<tr>
<td>Story Recall Test from the Adult Memory and Information Processing Battery (AMIPB)³: Immediate recall (Maximum score – score), Delayed recall (Maximum score – score)</td>
</tr>
</tbody>
</table>

Table 2: Memory composite analysis

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>Controls</th>
<th>Test Statistic (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite score*</td>
<td>-0.35 (0.99)</td>
<td>0.00 (0.73)</td>
<td>1.05 (1.83)</td>
<td>0.308</td>
</tr>
<tr>
<td>Percent impaired**</td>
<td>7 (14%)</td>
<td>2 (6%)</td>
<td>2.32 (1)</td>
<td>0.128</td>
</tr>
</tbody>
</table>

*p values from ANOVA analysis **p values from two tailed Pearson’s χ² test.

References:

